Neural restricted, FAC-sorted, human neural stem cells to treat traumatic brain injury

Grant Award Details

Neural restricted, FAC-sorted, human neural stem cells to treat traumatic brain injury

Grant Type: Early Translational II

Grant Number: TR2-01767

Project Objective: using Athymic rodents testing the development candidate feasibility of cell therapy to improve some of the symptoms caused by TBI (e.g, seizures).

Investigator:

Name:	Brian Cummings
Institution:	University of California, Irvine
Type:	PI

Disease Focus: Neurological Disorders, Trauma

Collaborative Funder: Maryland

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,517,767

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4/NCE

Grant Application Details

Application Title: Neural restricted, FAC-sorted, human neural stem cells to treat traumatic brain injury

Public Abstract: Traumatic brain injury (TBI) affects 1.4 million Americans a year; 175,000 in California. When the brain is injured, nerve cells near the site of injury die due to the initial trauma and interruption of blood flow. Secondary damage occurs as neighboring tissue is injured by the inflammatory response to the initial injury, leading to a larger area of damage. This damage happens to both neurons, the electrically active cells, and oligodendrocytes, the cell which makes the myelin insulation. A TBI patient typically loses cognitive function in one or more domains associated with the damage (e.g. attention deficits with frontal damage, or learning and memory deficits associated with temporal lobe/hippocampal damage); post-traumatic seizures are also common. Currently, no treatments have been shown to be beneficial in alleviating the cognitive problems following even a mild TBI.

Neural stem cells (NSCs) provide a cell population that is promising as a therapeutic for neurotrauma. One idea is that transplanting NSCs into an injury would provide "cell replacement"; the stem cells would differentiate into new neurons and new oligodendrocytes and fill in for lost host cells. We have successfully used "sorted" human NSCs in rodent models of spinal cord injury, showing that hNSCs migrate, proliferate, differentiate into oligodendrocytes and neurons, integrate with the host, and restore locomotor function. Killing the NSCs abolishes functional improvements, showing that integration of hNSCs mediates recovery. Two Phase I FDA trials support the potential of using sorted hNSC for brain therapy and were partially supported by studies in my lab. NSCs may also improve outcome by helping the host tissue repair itself, or by providing trophic support for newly born neurons following injury. Recently, transplantation of rodent-derived NSCs into a model of TBI showed limited, but significant improvements in some outcome measures. These results argue for the need to develop human-derived NSCs that can be used for TBI.

We will establish and characterize multiple "sorted" and "non-sorted" human NSC lines starting from 3 human ES lines. We will determine their neural potential in cell culture, and use the best 2 lines in an animal model of TBI, measuring learning, memory and seizure activity following TBI; then correlating these outcomes to tissue modifying effects. Ultimately, the proposed work may generate one or more human NSC lines suitable to use for TBI and/or other CNS injuries or disorders. A small reduction in the size of the injury or restoration of just some nerve fibers to their targets beyond the injury could have significant implications for a patient's quality of life and considerable economic impact to the people of California. If successful over the 3-year grant, additional funding of this approach may enable a clinical trial within the next five years given success in the Phase I FDA approved trials of sorted hNSCs for other nervous system disorders.

Statement of Benefit to California:

The Centers for Disease Control and Prevention estimate that traumatic brain injury (TBI) affects 1.4 million Americans every year. This equates to ~175,000 Californian's suffering a TBI each year. Additionally, at least 5.3 million Americans currently have a long-term or a lifelong need for help to perform activities of daily living as a result of suffering a TBI previously. Forty percent of patients who are hospitalized with a TBI had at least one unmet need for services one year after their injury. One example is a need to improve their memory and problem solving skills. TBI can also cause epilepsy and increases the risk for conditions such as Alzheimer's disease, Parkinson's disease, and other brain disorders that become more prevalent with age. The combined direct medical costs and indirect costs such as lost productivity due to TBI totaled an estimated $60 billion in the United States in 2000 (when the most recent data was available). This translates to ~$7.5 billion in costs each year just to Californians.

The proposed research seeks to generate several human neural-restricted stem cell lines from ES cells. These "sorted" neural-restricted stem cell lines should have greatly reduced or no tumor forming capability, making them ideally suited for clinical use. After verifying that these lines are multipotent (e.g. they can make neurons, astrocytes and oligodendrocytes), we will test their efficacy to improve outcomes in TBI on a number of measures, including learning and memory, seizure activity, tissue sparing, preservation of host neurons, and improvements in white matter pathology. Of benefit to California is that these same outcome measures in a rodent model of TBI can also be assessed in humans with TBI, potentially speeding the translational from laboratory to clinical application.

A small reduction in the size of the injury, or restoration of just some nerve fibers to their targets beyond the injury, or moderate improvement in learning and memory post-TBI, or a reduction in the number or severity of seizures could have significant implications for a patient's quality of life and considerable economic impact to the people of California. Additionally, the cell lines we have chosen to work with are unencumbered with IP issues that would prevent us, or others, from using these cell lines to test in other central nervous system disorders. Two of the cell lines have already been manufactured to "GMP" standards, which would speed up the translation of this work from the laboratory to the clinic. Finally, if successful, these lines would be potentially useful for treating a variety of central nervous system disorders in addition to TBI, including Alzheimer's disease, Parkinson's disease, stroke, autism, spinal cord injury, and/or multiple sclerosis.

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